A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging, Dose-Loading Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-42160443 as Adjunctive Therapy in Subjects With Inadequately Controlled, Moderate to Severe, Chronic Low Back Pain

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Primary ObjectivesThe primary objectives of this study are to evaluate the analgesic effect size over 12 weeks of several doses and dosage regimens of JNJ-42160443 compared with placebo in subjects with moderate to severe, chronic, low back pain (...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Muscle disorders
Study type	Interventional

Summary

ID

NL-OMON35462

Source
ToetsingOnline

Brief title
Pain therapy for patients with Chronic Low Back Pain

Condition

- Muscle disorders

Synonym
Low Back Pain

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: Janssen-Cilag B.V.

Intervention

Keyword: Low Back Pain, Monclonal antibody, Pain therapy

Outcome measures

Primary outcome

The primary efficacy evaluation is the average LBP-related pain intensity score at the end of the 12 week double-blind efficacy phase. The twice daily NRS LBP-related pain assessment will be collected using the subject e-diary and the question will be *Select the number that best describes your low back pain on average during the past 12 hours on a scale of 0 to 10, where 0=no pain and 10=pain as bad as you can imagine*. The baseline score is defined as the average LBP-related pain intensity scores averaged over the last 3 days of pain scores before random assignment. The end of the 12-week double-blind efficacy phase score is defined as the average LBP-related pain intensity scores averaged over the last 7 days of this phase.

The primary efficacy endpoint is the change from baseline to the end of the 12-week double-blind efficacy phase in the average LBP-related pain intensity score.

Secondary outcome

Key secondary efficacy evaluations are:

• ODI subscales and total score

• BPI Short Form pain severity and pain interference subscales

• PGA

Exploratory evaluations are:

• Rescue medication use

• Average pain intensity in the last 24 hours for up to 2 significant sources

of pain not related to LBP

• Daily sleep interference assessments

• MOS Sleep Scale subscales

• SF-36 Health Survey subscales

• Work Productivity Questionnaire

Study description

Background summary

Low back pain is a common cause of nonmalignant, chronic pain and represents one of the most significant socioeconomic health-related problems in developed countries.
Unless a diagnosis leading to curative medical or surgical procedures is established, the management of musculoskeletal nonmalignant chronic pain (chronic LBP being a predominant disease) remains in most cases symptomatic, directed primarily towards relief of pain, optimization of function, and minimization of disability. Pharmacologic treatment includes the following analgesics: non-steriodal anti-inflammatory drugs (NSAIDs), cyclooxygenase II (COX-II) inhibitors, acetaminophen (paracetamol), and opioids. Muscle relaxants, antidepressants, and occasionally sterioids (oral or epidural) are used. Despite the variety of available pharmacologic treatments for nonmalignant, chronic pain, many patients with chronic pain do not obtain adequate relief or experience unacceptable adverse events from existing treatments.

Nerve growth factor plays an important role in the generation of pain and hyperalgesia in several acute and chronic pain states, and anti-NGF therapy was associated with significant improvement in chronic pain from osteoarthritis. Although anti-NGF therapy for relief of chronic LBP has not been reported, NGF

expression was increased in intervertebral discs associated with pain on discography and was absent in intervertebral discs not associated with pain. Therefore, anti-NGF therapy may be effective in the treatment of chronic LBP as well as other chronic pain states.
This study will evaluate the analgesic efficacy, safety, and tolerability of several doses and dosage regimens of JNJ-42160443 in subjects with moderate to severe, chronic LBP that is not adequately controlled with standard pain therapies. This study will also provide information for dosing recommendations for future clinical studies.

Study objective

Primary Objectives
The primary objectives of this study are to evaluate the analgesic effect size over 12 weeks of several doses and dosage regimens of JNJ-42160443 compared with placebo in subjects with moderate to severe, chronic, low back pain (LBP) that is not adequately controlled by standard pain therapy, and to evaluate the safety and tolerability of multiple SC doses of JNJ-42160443 in this population.
Secondary Objectives
The key secondary objectives of this study are:
• To evaluate the efficacy of JNJ-42160443 compared with placebo as measured by back pain disability with subscales and total scores of the Oswestry Disability Index (ODI)
• To evaluate the efficacy of JNJ-42160443 compared with placebo as measured by the pain severity and pain interference subscales and total scores from the Brief Pain Inventory (BPI) Short Form
• To evaluate the efficacy of JNJ-42160443 compared with placebo as measured by the Patient Global Assessment (PGA)
Other secondary objectives are:
• To evaluate the pharmacokinetics of JNJ-42160043 after multiple dose administrations of JNJ 42160443. A population PK approach will be used to characterize the disposition characteristics of JNJ 42160443 in this study.
• To evaluate the immunogenicity (antibodies to JNJ-42160443) associated with JNJ 42160443 treatment
• To evaluate the long-term efficacy, safety, and tolerability of JNJ-42160443 in this subject population during the 92-week double-blind extension phase
Exploratory Objectives
The exploratory objectives of this study are:
• To evaluate the efficacy of JNJ-42160443 compared with placebo as measured by rescue medication use
• To investigate the effects of JNJ-42160443 on changes in functional status (including physical functioning) and well-being with subscales of the Short Form 36 (SF-36*) Health Survey
• To investigate the effects of JNJ-42160443 on dimensions of sleep and daytime somnolence using a daily sleep interference question and the Medical Outcomes Study (MOS) Sleep Scale
• To investigate potential biomarker development by biochemical analysis of

blood samples
• To explore PK/pharmacodynamic (PD) modeling using pooled data from other JNJ 42160443 studies

Study design

This is a randomized, double-blind, placebo-controlled, dose-ranging, dose-loading study evaluating the analgesic efficacy, safety and tolerability of JNJ-42160443 at several doses and dosage regimens in subjects with moderate to severe, chronic, LBP that is not adequately controlled by standard pain therapy. The study consists of a 3-week screening phase, a 12 week double blind efficacy phase, a 92 week double blind extension phase, and a 26 week posttreatment phase. The screening phase may be extended up to 3 months to meet the contraception inclusion criteria for women, but baseline safety evaluations must be performed within 3 weeks before the first dose of study drug. Approximately 360 subjects will be enrolled and randomly assigned to receive either placebo or 1 of 4 JNJ 4216043 treatment regimens, 72 subjects in each treatment group.
The study duration will be approximately 41 weeks (3-week screening phase, 12-week double-blind efficacy phase, and 26-week posttreatment phase for immunogenicity evaluations) for a subject who does not continue in the double-blind extension phase. The study duration for a subject who completes both the double-blind efficacy and extension phases will be approximately 133 weeks (3-week screening phase, 12 week double-blind efficacy phase, 92-week double blind extension phase, and 26-week posttreatment phase for immunogenicity evaluations).

Intervention

Subjects will be randomly assigned to receive placebo or 1 of 4 JNJ-42160443 treatment regimens: 1 mg every 4 weeks, 3 mg every 4 weeks, an initial 6 mg loading dose followed by 3 mg every 4 weeks, and 10 mg of every 4 weeks. Within each cohort of approximately 90 subjects, subjects will be randomly assigned to treatment in a 4:1 ratio to receive placebo or 1 of 4 JNJ 42160443 treatment regimens (active treatment:placebo 72:18 subjects in each treatment cohort). Doses of JNJ-42160443 or placebo will be administered as a SC injection into the thigh. An alternative administration site, to be used only in the event that the study drug cannot be administered into the thigh, is the abdomen (avoiding the area 2 inches around the navel). JNJ-42160443 will be provided in vials containing 1 mL of solution (10 mg/mL). Doses will be administered by volume (eg, 1 mg=0.1 mL, 3 mg=0.3 mL, 6 mg=0.6 mL, 10 mg=1 mL). Each of the 4 cohorts will have a different dosing volume and the placebo dosing volume will match its treatment cohort dosing volume. A scheduled PK blood sample must be collected before administration of any JNJ 42160443 dose of study drug. The method(s) of contraception used by each subject or their partner must be documented before administration of any dose of study drug. A pharmacy manual

containing detailed information about the dose preparation and administration instructions will be provided to each study site.
During the double-blind extension phase, subjects will remain in the same blinded treatment group to which they were initially randomly assigned, and will receive the same volume of injection (including placebo subjects).

Study burden and risks

Burden for the patients
- In the first 3 months, the patient will be asked to complet an e-diary twice daily to report pain score, score sleep quality and rescue medication.
- Patient visits the site monthly for administration of study medication.
During these visits a number of questionnaires has to be completed and neurological tests will be done. After administration of study medication, the patient has to stay in the hospital for another 30 minutes under supervision of the studystaff. These visits can therefore last about 1.5 to 2 hours.

Possible risks and adverse events : see E9

Benifits : possible pain relief with the study drug

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Man or woman, 18 - 70 years of age
• Documented clinical diagnosis of moderate to severe, chronic, LBP that is inadequately controlled with prior analgesic therapy and must have been present (by history) for at least:
- *20 days/month
- *3 hours/day
- *6 months
• Have an average pain intensity score of *5 averaged over the last 3 days of pain scores before randomization (Day 1) using an 11-point NRS, where the minimum single assessment score is *2
• Must be receiving at least 1 of the following analgesic regimens:
- Stable dose of NSAIDs for a minimum of 5 days each week for the 4 weeks before screening
- Stable dose of immediate-release opioids for a minimum of 5 days each week for the 4 weeks before screening, but not exceeding 200 mg oral morphine equivalents per day (refer to Attachment 16, Equianalgesic Potency Conversion Table)
- Stable dose of long-acting opioids for the 4 weeks before screening, but not exceeding 200 mg oral morphine equivalents per day (refer to Attachment 16, Equianalgesic Potency Conversion Table); subjects receiving long acting opioids who use immediate-release opioids for breakthrough pain must not exceed, on average, more than 2 doses of immediate-release opioids per day during any 7-day period
• Have a MMSE score of *26 at screening
• Subjects who are sexually active must consent to utilize and document a medically acceptable and highly effective (*1% per year failure rate) method of contraception throughout the entire study from screening through 6 months after the last dose of study drug
- Medically acceptable, highly effective methods of contraception that may be used by the subject and/or partner include hormonal oral, transdermal, progestin implant, or injectable contraception, or intrauterine device (IUD), tubectomy or vasectomy
- For women of childbearing potential, contraception must be consistently used for at least 3 months before the first dose of study drug. The screening phase may be extended up to 3 months to meet this requirement, but baseline safety evaluations must be performed within 3 weeks before the first dose of study drug.
- Subject or partner may also be postmenopausal (states having not experienced a menstrual period for a minimum of 12 months) or surgically sterile
- Further, subjects must agree to not donate sperm or eggs or attempt conception (pregnancy) from screening through 6 months after the last dose of study drug
• Women of childbearing potential must have a negative serum * human chorionic gonadotropin (* hCG) pregnancy test at screening and a negative urine * hCG pregnancy test

at randomization (Day 1)
• Medically stable on the basis of physical examination, medical history, vital signs, clinical laboratory tests, and 12-lead ECG performed at screening
• Willing/able to comply with study procedures and evaluations specified in the protocol, including the completion of all PRO scales and questionnaires
• Willing/able to adhere to the prohibitions and restrictions specified in this protocol
• Subjects must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study.
• To participate in the optional pharmacogenomic component of this study, subjects must have signed the informed consent form for pharmacogenomic research indicating willingness to participate in the pharmacogenomic component of the study (where local regulations permit). Refusal to give consent for this component does not exclude a subject from participation in the clinical study.
To enter the double-blind extension phase, subjects must meet the following criteria:
• Must have completed the double-blind efficacy phase of the study
• Women of childbearing potential must have a negative urine * hCG pregnancy test at the end of the double-blind efficacy phase (Week 13)

Exclusion criteria

• History within the past year of any of the following:
- Seizure disorder
- Intrathecal therapy, epidural therapy, and ventricular shunts
- Mild or moderate traumatic brain injury
- Stroke
- Transient ischemic attack
- Meningitis
• History of brain injury within the past 15 years consisting of *1 of the following, or with residual sequalae suggesting transient changes in consciousness:
- Brain contusion
- Intracranial hematoma
- Either unconsciousness or posttraumatic amnesia lasting more than 24 hours
• History of epilepsy or multiple sclerosis
• Active diagnosis of fibromyalgia, complex regional pain syndrome (including reflex sympathetic dystrophy or causalgia), acute spinal cord compression, bowel or bladder dysfunction as a result of cauda equine compression, back pain caused by secondary infection, or pain caused by confirmed or suspected neoplasm
• Any new or unresolved neurologic deficits, including progressive deficits, within 6 months before screening. Transient neurologic deficits that are resolved within this period or those related to their lumbosacral radiculopathy can be allowed if approved by the investigator.
• Active peripheral neuropathy, paresthesia, or dysesthesia, or any other previously diagnosed neurologic condition causing the above noted symptoms, except those related to their lumbosacral radiculopathy
• Have undergone a surgical procedure for LBP within 6 months before the screening visit or

planned surgery for LBP during the 12-week double-blind efficacy phase
• History of a major surgical procedure (ie, involving general or regional anesthesia), significant trauma, or a nonhealing wound or ulcer within 3 months before the screening visit
• Have had nerve or plexus block, including epidural steroid injections or facet blocks, within the 4 weeks before the screening visit
• History of diabetes mellitus or laboratory results consistent with diabetes mellitus (ie, fasting plasma glucose *126 mg/dL or *7 mmol/L)
• Have a Body Mass Index (BMI) of *35 kg/m2
• History of drug or alcohol abuse within the past 5 years
• History of or suspected human immunodeficiency virus (HIV) infection (Note: HIV testing is not required for this study)
• Severe depression as defined by a score of *29 on the BDI-II at screening
• Any other chronic pain condition that, in the investigator*s opinion, would interfere with the assessment of chronic LBP (eg, OA, rheumatoid arthritis, postherpetic neuralgia)
• History of malignancy within the past 2 years, with the exception of basal cell carcinoma that has been successfully treated
• Uncontrolled cardiovascular disease or hypertension (repeated systolic blood pressure (SBP) >160 mmHg or diastolic blood pressure (DBP) >100 mmHg
• Prior treatment with experimental NGF inhibitor therapy
• Known allergies, hypersensitivity, or intolerance to JNJ-42160443 or its excipients or mammalian cell-derived (ie, Chinese hamster ovary) products (refer to Section 14.1, Physical Description of Study Drug, for a list of JNJ-42160443 excipients)
• Received an investigational drug or used an investigational medical device within 30 days before the screening visit (or 5 half-lives of the investigational drug, whichever is longer) or are currently enrolled in an investigational study
• Pregnant or breast-feeding
• Pending litigation due to chronic pain or disability
• Any condition that, in the opinion of the investigator, would compromise the well being of the subject or the study or prevent the subject from meeting or performing study requirements
• Employees of the investigator or site, with direct involvement in the proposed study or other studies under the direction of that investigator or site, as well as family members of the employees or the investigator

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial

Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-09-2009
Enrollment:	40
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	nog niet gekend
Generic name:	nog niet gekend

Ethics review

Approved WMO Date:	14-10-2009
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-12-2009
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	30-12-2009
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	09-02-2010
Application type:	Amendment

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2009-009857-17-NL
ClinicalTrials.gov	NCT00973024
CCMO	NL27682.068.09